Cytostatic drugs and radiation. The alkylating agents react directly with DNA and induce AML which often presents as myelodysplasia with unbalanced aberrations, primarily loss of chromosome material. Cytostatic agents targeting DNA-topoisomerase II, frequently administered together with alkylating agents or cisplatin, induce the same type of leukemia. In addition, they often induce another type with a more rapid onset and with specific balanced chromosome aberrations rarely observed after therapy with alkylating agents alone. All of the most important chromosome aberrations found in de novo AML are now also found in therapy-related AML (t-AML); thus, t-AML may serve as a model in the search for mechanisms leading to the development of AML in general. Unbalanced chromosome aberrations with partial deletions or with loss of whole chromosomes may develop as a result of alkylation of DNA or other cellular targets. Balanced chromosome aberrations, on the other hand, may develop as illegitimate recombinations related to the activity of DNA-topoisomerase II. The balanced translocations contribute to malignant transformation by the formation of abnormal chimeric genes, whereas deletions may contribute by the loss of putative tumor suppressor genes. In either situation, the chromosome changes provide the altered cells with a proliferative advantage compared with normal cells.

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Little was known previously about the mechanisms leading to the development of chromosome aberrations in cancer in general. For example, do the characteristic aberrations arise more specifically in certain chromosomes or certain chromosome bands or do they arise completely at random with selection of those aberrations providing the cell with a proliferative advantage? Their role as direct causative factors or alternatively as playing only a secondary role in tumor progression or no role at all in malignant transformation has also been controversial.

Gain and loss of a whole chromosome is traditionally regarded as the result of nondisjunction at mitosis, whereby one daughter cell loses a chromosome that may be gained by the other daughter cell. Other mechanisms may also contribute to aneuploidy. Chromosome loss may be the result of formation of micronuclei and chromosome lagging during anaphase. In therapy-related myelodysplasia (t-MDS) and therapy-related AML (t-AML), deletions of the long arms of chromosomes 5 and 7 may often result in subsequent loss of the whole chromosome. In yeast, loss of the telomere was recently shown to result in a dramatic increase in the loss of the whole chromosome during the following five cell cycles. Exclusive gain of chromosomes may be the result of reduplication. Structural chromosome aberrations with breakage at characteristic bands have previously been related to the existence of fragile sites within the genome, either hereditary or constitutional. Finally, cytostatic drugs such as melphalan and etoposide have been shown to be direct inducers of nonrandom chromosome breaks in cultured human lymphocytes.

In AML, most cases arise de novo with unknown causative factors. However, 10% to 20% of cases of AML observed in many institutions are now secondary or therapy related. In these cases, the leukemogenic agent, most often a cytostatic drug, is chemically well-defined and is administered in a known dose, at a known time, and with a mechanism of action, particularly in cell killing, that...
Table 1. Balanced and Unbalanced Chromosome Aberrations Observed in Both De Novo AML and Leukemia Related to Therapy With Cytostatic Agents

<table>
<thead>
<tr>
<th>Unbalanced Aberrations Observed in De Novo AML and in t-AML After Alkylating Agents</th>
<th>Balanced Aberrations Observed in De Novo AML and in t-AML After Drugs Targeting at DNA-Topoisomerase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(7q)</td>
<td>t(4;11)(q21;q23)</td>
</tr>
<tr>
<td>del(5q)</td>
<td>t(6;11)(q27;p15)</td>
</tr>
<tr>
<td>del(5q)</td>
<td>t(9;11)(p22;q23)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>t(11;19)(q23;p13)</td>
</tr>
<tr>
<td>del(12p)</td>
<td>t(3;21)(q26;q22)</td>
</tr>
<tr>
<td>del(12p)</td>
<td>t(8;21)(q22;q22)</td>
</tr>
<tr>
<td>del(20q)</td>
<td>t(15;17)(q22;q12)</td>
</tr>
<tr>
<td>del(20q)</td>
<td>t(8;18)(p11;p13)</td>
</tr>
<tr>
<td>del(20q)</td>
<td>inv(16)(p13q22)</td>
</tr>
<tr>
<td>-18</td>
<td>t(6;9)(p23;q34)</td>
</tr>
<tr>
<td>dup(1q)†</td>
<td></td>
</tr>
</tbody>
</table>

* Most often observed in de novo and therapy-related acute lymphoid leukemia, but also seen in biphenotypic acute leukemia and in single cases of AML.
† In t-AML, most often observed in only a subclone of cells.
‡ Gain of the long arm of chromosome no. 1 in t-AML is closely related to concomitant loss of the long arm of chromosome no. 7 caused by the unbalanced translocation −7, +der(7)t(1;7)(q11;q11).

Table 2. Structure and Function of Genes Rearranged in the Balanced Chromosome Aberrations in Acute Myeloid and Lymphoid Leukemia

<table>
<thead>
<tr>
<th>Genes</th>
<th>Chromosome Band</th>
<th>Structural Motifs</th>
<th>Proposed Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL (HRX or ALL1)</td>
<td>11q23</td>
<td>AT hook, zinc finger, trithorax homology</td>
<td>DNA binding, gene regulation</td>
</tr>
<tr>
<td>AF4* or MLLT2</td>
<td>4q21</td>
<td>Nuclear localization signal</td>
<td>Unknown</td>
</tr>
<tr>
<td>AF9* or MLLT3</td>
<td>9p22</td>
<td>Nuclear localization signal</td>
<td>Unknown</td>
</tr>
<tr>
<td>ENL* or MLLT1</td>
<td>19p13</td>
<td>Nuclear localization signal</td>
<td>Unknown</td>
</tr>
<tr>
<td>AML1 or CBFA1</td>
<td>21q22</td>
<td>runt homology</td>
<td>DNA binding, gene regulation</td>
</tr>
<tr>
<td>EAP</td>
<td>3q26</td>
<td></td>
<td>Ribosomal protein</td>
</tr>
<tr>
<td>ETO, CDR, or MTGB</td>
<td>8q22</td>
<td>Zinc finger</td>
<td>DNA binding, gene regulation</td>
</tr>
<tr>
<td>PML</td>
<td>15q22</td>
<td>Zinc finger</td>
<td>DNA binding, gene regulation</td>
</tr>
<tr>
<td>RARA</td>
<td>17q12</td>
<td>Zinc Finger</td>
<td>DNA binding, gene regulation (retinoic acid receptor a)</td>
</tr>
<tr>
<td>MYH11</td>
<td>16p13</td>
<td>α-Helix coiled coil (myosin heavy chain gene)</td>
<td>—</td>
</tr>
<tr>
<td>CBFB1 or PEBP2β</td>
<td>16q22</td>
<td></td>
<td>Transcriptional modulator</td>
</tr>
<tr>
<td>DEC</td>
<td>6p23</td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td>CAN</td>
<td>9q34</td>
<td>Helix-loop-helix</td>
<td>DNA binding, gene regulation</td>
</tr>
</tbody>
</table>

* Share sequence homology and/or common motifs.
† CBFA and B form dimers.

Table 3. Cytostatic Agents Shown to be Leukemogenic in Human

<table>
<thead>
<tr>
<th>Alkylating Agents</th>
<th>Drugs Poisoning DNA-Topoisomerase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechloretamine</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Teniposide</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>4-Epidoxorubicin</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Dihydroxybusulfan</td>
<td>Roxane</td>
</tr>
<tr>
<td>Prednimustine</td>
<td>Bimolane*</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Lomustine</td>
</tr>
<tr>
<td>Semustine</td>
<td>Semustine</td>
</tr>
</tbody>
</table>

* Has not yet been shown to target DNA-topoisomerase II, but belongs to the group dioxopiperazine derivatives with such a mechanism of action.

RISK OF LEUKEMIA AFTER DIFFERENT TYPES OF CYTOSTATIC DRUGS

For more than two decades it has been known that there is an increased risk of MDS and AML after therapy with alkylating agents. In fact, almost all alkylating agents in clinical use today have been shown to be leukemogenic in well-defined patient cohorts (Table 3). Increasing age has been shown to predispose to development of t-MDS and t-AML in patients with Hodgkin’s disease treated with alkylating agents, and the risk has been shown to increase directly proportional with dose. A direct comparison of the risks for each of the different alkylating agents is difficult, because only a very few studies have compared the effect of more than one drug prospectively. However, in many cohorts of patients treated with different alkylating agents, the cumulative risks have been shown to increase by 0.5% to 1% per year from 2 years after start of chemotherapy to at least 6 to 8 years after cessation of therapy. In the same studies, the relative risk (the ratio between the observed number of
t-AML and the expected number of de novo AML has often been greater than 100. This indicates that almost all cases of t-AML observed are directly induced by therapy because only 1 of 100 cases or more of t-AML could be expected to represent a coincidental case of de novo AML.

An increased risk of AML after therapy with a cytostatic drug not belonging to the alkylating agents and not reacting directly with DNA was first reported for Razo~ane, a dioxo-1,2-piperazine derivative targeting DNA-topoisomerase II (Table 3). The drug was previously used mainly in the treatment of psoriasis. Quite recently, another drug, Bimolane, belonging to the same chemical group of cytostatic agents and also used for psoriasis, has been demonstrated as leukemogenic in Chinese studies. Other cytostatic agents targeting DNA-topoisomerase II have also been demonstrated to be leukemogenic (Table 3). The epipodophyllotoxins, etoposide and teniposide, have been shown to induce AML in cohort studies, most often in combination with cisplatin or alkylating agents. The results of two larger case-control studies suggest that the anthracycline, doxorubicin, may be leukemogenic.

In childhood cancer, the drug was often administered in combination with alkylating agents, and in ovarian cancer in combination with cisplatin. In childhood cancer and in germ cell tumors, it was suggested that cytostatic drugs with the two mechanisms of action, a direct covalent binding to DNA or other cellular targets and an inhibition of DNA-topoisomerase II, could have a synergistic effect in leukemogenesis. Also another anthracycline, 4-epi-doxorubicin, was shown to be leukemogenic if combined with cisplatin or an alkylating agent. In many of these studies, an extremely high risk of leukemia was observed with an accelerated development of the disease.

CYTOGENETIC CHARACTERISTICS OF THERAPY-RELATED LEUKEMIA

The fact that most cases of t-MDS and t-AML have unbalanced chromosome aberrations with loss of whole chromosomes no. 5 and 7 or of parts of their long arms was first demonstrated in 1977. This finding has subsequently been confirmed, and the loss or deletion of chromosomes no. 5 and 7 has been closely associated with previous therapy with alkylating agents (Table 1). The breakpoints for the deletions are variable, but a common chromosome region, the so-called critical region, is almost always deleted. For chromosomes no. 5, the critical region is 5q31.42 Deletions of various parts of the short arm of chromosomes no. 12 and 17 and of the long arm of chromosome no. 20, and loss of a whole chromosome no. 18 as well as gain of a whole chromosome no. 8 or of the long arm of chromosome no. 1 have also been observed as nonrandom aberrations in t-MDS and t-AML related to therapy with alkylating agents (Table 1). Unlike the many aberrations with loss of chromosome material, a gain of chromosome no. 8 is most often observed as an inconsistent aberration present in only a subclone of cells, and gain of another copy of the long arm of chromosome no. 1 is closely related to a concomitant loss of the long arm of a chromosome no. 7 because of an unbalanced translocation between the two chromosomes.

In the initial studies demonstrating an increased risk of t-AML after therapy with etoposide and teniposide, the predominant finding was rearrangement of the long arm of chromosome no. 11 rather than deletions of chromosomes no. 5 and 7. Subsequently, balanced translocations specifically involving chromosome bands 11q23 and 21q22 in t-AML (Table 1) were found to be significantly associated with previous therapy with various drugs targeting DNA-topoisomerase II, primarily the epipodophyllotoxins and the anthracyclines. On the other hand, both studies showed that unbalanced rearrangements of the same two bands were most often associated with therapy with alkylating agents alone or with radiotherapy. In addition to the various balanced translocations involving chromosome band 11q23, primarily t(6;11), t(9;11), and t(11;19), and the translocations t(8;21) and t(3;21) involving chromosome band 21q22, other balanced aberrations such as inv(16), t(8;16), t(15;17), and t(6;9) have been observed in t-AML after previous therapy with drugs targeting DNA-topoisomerase II (Table 1).

Translocations to chromosome band 11q23 predominate in children with t-AML after therapy with the epipodophyllotoxins for acute lymphoid leukemia (ALL), the t(15;17) is frequent in Chinese patients treated for psoriasis with bimolane, and there may be an excess of cases of t-AML with balanced translocations to chromosome band 21q22, in particular t(3;21), after therapy with doxorubicin. However, at present it is not completely clear to what extent age, race, and type of drug predispose to development of each of the specific balanced translocations.

In most of the studies demonstrating an increased risk of t-AML after therapy with a drug targeting DNA-topoisomerase II, these drugs were administered in combination with either cisplatin or an alkylating agent, or of a drug targeting DNA-topoisomerase II, whereas the later occurring leukemias, showing deletions of chromosomes no. 5 or 7 or a normal karyotype, may represent leukemias induced by the alkylating agents or cisplatin used in the combined treatment.

CLINICAL CHARACTERISTICS OF LEUKEMIAS PRESENTING UNBALANCED AND BALANCED CHROMOSOME ABBERRATIONS

Major clinical differences are observed between leukemias with unbalanced chromosome aberrations and leukemias with balanced aberrations, whether they arise de novo or are therapy-related (Table 4), emphasizing that a distinction between these two types of chromosome abnormality in AML is of biologic importance. AML patients with unbalanced aberrations, in particular deletions of chromosomes no. 5 and 7, are often older, in many cases have a history of past exposure to mutagenic chemicals, and at present may be of any French-American-British (FAB) subtype except for M3, and generally respond poorly to intensive antileukemic chemotherapy. It is of interest that many patients with erythroleukemia (FAB subtype M6) show the same clinical and cytogenetic features.

For de novo leukemias with balanced translocations (Ta-
able 4), translocations to chromosome band 11q23 predominant in neonatal leukemia.56 The MLL gene is rearranged in these 11q23 translocations and the leukemias are most often of FAB subtype M4 or M5. The t(8;21), t(15;17), and inv(16) are also observed more frequently in children and in younger adults with AML and in the same way are closely related to the specific FAB subtypes: M2, M3, and M4EO, respectively.3 MDS is rarely observed in such patients, and the leukemias generally respond favorably to intensive antileukemic chemotherapy.14-16 Whereas the increasing incidence with age of de novo AML with unbalanced chromosome aberrations could be related to a life-long exposure of the general population to irradiation and to chemical carcinogens, the less age-dependent development of de novo AML with balanced chromosome aberrations could point to alternative mechanisms in leukemogenesis, for instance, spontaneous illegitimate recombination during the normal activity of DNA-topoisomerase II.

MECHANISMS INVOLVED IN THE DEVELOPMENT OF CHROMOSOME ABERRATIONS IN AML

It has been an open question whether the chromosome aberrations observed in t-AML arise as a primary direct result of an exposure of hematopoietic cells to cytostatic drugs or whether they develop as a secondary phenomenon. A comparison of the results of two recent studies from Structure et Mutagenese Chromosomique, Institute Curié, Paris, France22,23 could help to clarify this question. In the two in vitro studies, phytohemagglutinin-stimulated normal human lymphocytes were exposed to an alkylating agent, melphalan,23 or to the DNA-topoisomerase II targeting epipodophyllotoxin, etoposide25 in short-term culture, and cytogenetic studies were performed (Table 5). In cells exposed to melphalan, deletions predominated, whereas an excess of reciprocal translocations was observed after etoposide exposure. A slight excess of deletions of chromosome no. 7 was observed after melphalan, and chromosome band 11q22 was one of several bands showing some propensity for rearrangement after etoposide. The techniques used, the drug concentrations, and the time of exposure were comparable although not completely identical in the two studies. The experience in t-AML demonstrating a strong association between exposure to alkylating agents and development of unbalanced chromosome aberrations, and exposure to drugs targeting DNA-topoisomerase II and the development of balanced chromosome aberrations thus appears to be reflected in the short-term culture of normal human lymphocytes exposed to these two classes of drugs. These findings support the proposal that the chromosome aberrations observed in t-AML are in fact primary and direct effects of an exposure of hematopoietic cells to cytostatic agents.

In de novo AML, an almost equal frequency of gain or loss of whole chromosomes is observed, suggesting that these aberrations could develop by nondisjunction. In t-AML related to therapy with alkylating agents, on the other hand, loss of whole chromosomes predominates,54-56 particularly if only those aberrations are considered that are present in all abnormal mitoses, the so-called consistently present aberrations.50 This suggests that cell damage by alkylation leads to chromosome loss, for instance by lagging, rather than to development of nondisjunction.

An increased frequency of sister chromatid exchange and quadriradials has been observed after poisoning the DNA-topoisomerase II with epipodophyllotoxins.57,58 Furthermore, topoisomerase II is known to play a role in mitotic chromosome condensation and in segregation of replicated daughter chromosomes.59,60 The cytogenetic results from t-AML and from in vitro culture of normal human lymphocytes exposed to melphalan and etoposide now suggest that DNA-topoisomerase II is also involved in the development of balanced chromosome aberrations in general. The enzyme induces transient, enzyme-bridged double-strand breaks of DNA, and religation of these breaks is inhibited by the epipodophyllotoxins and by many anthracyclines.59,60 Inhibition of religation of DNA double-strand breaks could facilitate illegitimate cross-over recombinations between two different chromosomes, and nonhomologous recombination linked to the activity of topoisomerase II has in fact been observed at "hot spots" at chromosomal loop attachment sites.61 Quite recently, sequence analysis of two cases of AML with t(15;17)62 and one case of AML with t(9;11)63 has shown potential DNA-topoisomerase II-binding sites near the breakpoints for the translocations, and in the patient with t(9;11) specific heptamers flanking the breakpoints have also been identified. These findings provide further support for the hypothesis that DNA-topoisomerase II could be directly

<table>
<thead>
<tr>
<th>Table 4. Clinical and Cytologic Characteristics of Different Cytogenetic Subtypes of AML</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Older patients, often mutagen exposed or treated with alkylating agents, often preceding MDS, of all FAB subtypes except M3 and with a poor response to intensive antileukemic chemotherapy.</td>
</tr>
</tbody>
</table>

Data compiled from two studies from Structure et Mutagenese Chromosomiques, Institute Curié, Paris, France.59,60 Abbreviation: NR, not reported.

<table>
<thead>
<tr>
<th>Table 5. Chromosome Studies of Lymphocytes Exposed In Vitro to Melphalan or Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Type of Chromosome Aberration Observed</td>
</tr>
<tr>
<td>Deletions</td>
</tr>
<tr>
<td>Unbalanced or complex rearrangements</td>
</tr>
<tr>
<td>Reciprocal translocations</td>
</tr>
<tr>
<td>Inversions</td>
</tr>
</tbody>
</table>

Data compiled from two studies from Structure et Mutagenese Chromosomiques, Institute Curié, Paris, France.59,60 Abbreviation: NR, not reported.

* Phytohemagglutinin-treated cells (72 hours of culture) exposed to Melphalan at 6 μg/mL for 5 hours.
† Phytohemagglutinin-treated cells (48 hours of culture) exposed to Etoposide at 85 μmol/L for 1 hour.
involved in the development of the balanced translocations. The observation that each of the cytostatic drugs or groups of drugs targeting DNA-topoisomerase II may induce AML with some specific translocations predominating, and not the whole spectrum of balanced aberrations, may be related to a preference of the individual drugs for cleavage at different genomic sites.  

THE ROLE OF CHROMOSOME ABBERRATIONS IN LEUKEMIC TRANSFORMATION

Numerous experimental data related to carcinogenesis and the elegant studies of genetic alterations during development of colorectal cancer by Vogelstein et al indicate that malignant transformation is a multistep process. In AML, the characteristic chromosome aberrations are often observed in all leukemic cells, even at the earliest clinical stage of the disease. For this reason, the abnormal chimeric genes derived from the balanced chromosome translocations (Table 2) and the putative tumor suppressor genes on the long arms of chromosomes no. 5 and 7 are likely to represent primary but alternative steps in leukemogenesis. The gene of importance is often tumor suppressor genes, because most of these abnormalities of chromosome band 11q23. In acute leukemia, the balanced aberrations involving 11q23 lead to rearrangement of the MLL gene within a small region in almost all cases, whereas, in the various deletions of band 11q23, the loss of a region proximal to the MLL gene that includes the NCAM gene seems to be the critical molecular event.

The presence in many cases of additional, secondary recurring chromosome aberrations suggests that other genetic alterations are superimposed on the primary changes to lead to a fully malignant phenotype. The genes affected by the secondary chromosome abnormalities in t-AML probably are often tumor suppressor genes, because most of these aberrations are deletions (Table 1). The differences in many of the clinical features between the two general types of leukemia support the hypothesis of a difference in genetic origin.

Presumably, those cases of AML with an apparently normal karyotype, both de novo and therapy-related, have sustained genetic changes of the same type as observed in cases with chromosome abnormalities, changes that are undetected with our present cytogenetic techniques. Thus, characteristic rearrangements of genes or pairs of genes such as ABL-BCR, RARA-PML, AML1-ETO, and MLL have been observed in patients with myeloid leukemia who have an apparently normal karyotype.  

With the increasing availability of more sophisticated tools and understanding of drug-chromatin interactions, it should be possible to analyze further the mechanisms leading to balanced and to unbalanced chromosome aberrations in t-AML. These insights should allow a more comprehensive understanding of the events leading to development of leukemia in general.

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The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation

J Pedersen-Bjergaard and JD Rowley